AAAA I Ask The Expert
8/16/11

Q:

Thank you for your help. I have a patient whose mother has lupus. The patient is a teen ager and complained of hives when going outside, even when not in the sun. I sent CBC, ANA, ds DNA, C4, ESR, and CRP. All of these were WNL except for low C4 at 14. I repeated this several weeks later and was 11. Thoughts when all the other labs are OK? Thanks so much.

A:

Thank you for your recent inquiry.

As you can see from the abstract copied below, there are two separate genes that control the synthesis of C4. These are highly homologous. Within each of these genes there can be duplications, deletions, or inactivating mutations. The frequency of these make the interpretation of a low serum complement difficult. In fact, a decreased concentration of C4 is relatively common, occurring in up to 2% of the population.

It is also highly possible, since 15% of patients with systemic lupus have a low C4, your patient's mother may have genetic mutations in both genes, and the child may have inherited only a single gene abnormality. A deficiency in the C4A gene is a risk factor for SLE. On the other hand, C4B deficiency is more common and can occur, as noted, in up to 2% of the population.

As noted above, certainly C4 deficiencies are associated with SLE, but in such cases, one usually sees the usual autoantibodies (although anti-dsDNA antibodies occur less frequently). In addition, patients with C4 deficiency can be subject to infections.

Partial C4 deficiency with levels consistent with that seen in your patient are very common, and in the vast majority of instances they are not associated with any clinical manifestations. To my knowledge, urticaria when going outdoors is not known to be related with deficiencies in C4. However, it should not be difficult to detect immune complexes in the urticarial lesions if you wanted to pursue this further. But in the absence of any other laboratory finding suggesting systemic lupus or vasculitis, it is more than likely that the hives are unrelated.

In summary, partial C4 deficiencies are quite common, and in most cases arr not a sign of any disease state. Those patients who do have a clinically significant C4 deficiency and have systemic lupus erythematosus present with more prominent disease than is seen in your patient, and demonstrate other serologic abnormalities associated with lupus.

The simplest way to determine whether the urticaria was in any way related to the C4 deficiency would be to obtain a biopsy of the urticaria and investigate with histology and immunofluorescence for the presence of complement and immune complexes.

Thank you again for your inquiry and we hope this response is helpful to you.

Abstract:
G J O'Neill, et al, Two HLA-linked loci controlling the fourth component of human complement
PNAS October 1, 1978 vol. 75 no. 10 5165-5169
Abstract
An electrophoretic polymorphism of the fourth component of human complement (C4) is described. Three patterns of bands of C4 were observed in EDTA plasma from a panel of unrelated blood donors and family

members by using the technique of immunofixation electrophoresis. These patterns consisted of four fast-moving anodal bands (F), four slow-moving cathodal bands (S), or a combination of both the F and S bands (FS). The C4 patterns of bands were observed in EDTA plasma and not in serum. Family studies showed that this polymorphism of C4 did not segregate with HLA histocompatibility genes in a fashion governed by two codominant alleles at a single genetic locus. The family data are in agreement with the hypothesis that two different genetic loci control the electrophoretic patterns of C4. One locus controls the presence (F) or absence (f0) of the four anodal (F) bands and the other controls the presence (S) or absence (s0) of the four cathodal (S) bands. The C4F and C4S loci are both closely linked to HLA-B.

Sincerely,
Phil Lieberman, M.D.